THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 22.01.2003 in respect of Patent Application No. 82/MUM/2003 of Torrent Pharmaceuticals Ltd., a company incorporated under the Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad – 380 009, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 09 th day of October 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

M.A. Haafeez.

(M.A. HAAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT

(See Sections 5(2), 7, 54 and 135 AND Rule 33A)

(1) We, **TORRENT PHARMACEUTICALS LTD.**, a company incorporated under Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad-380 009, India,

(2) hereby declare –

(a) We are in possession of an invention titled

"NOVEL DOSAGE FORM"

(b) Provisional Specification relating to this invention is filed with this application;

(c) that there is no lawful ground of objection to the grant of a patent to us.

ORIGINAL

(3) further declare that the inventor for the said invention is:

NADKARNI, Sunil, Sadanand, an Indian citizen, of Torrent Research Centre, Torrent Pharmaceuticals Ltd., Bhat, Gandhinagar, Gujarat, India .

(4) We claim priority from the application(s) filed in the following convention country, particulars of which are as follows:

NIL

(5) That we are the assignees of the true and first inventor.

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
E 556, Greater Kailash II,
New Delhi - 110 048, India.
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(7) The following declaration was given by the true and first inventors:

I, **NADKARNI, Sunil, Sadanand**; an Indian citizen, of Torrent Research Centre, **Torrent Pharmaceuticals Ltd.**, Bhat, Gandhinagar, Gujarat, India; the true and first inventor declare the applicants herein are my assignees:

82/mum/2003
22/1/2003

SUNIL SADANAND NADKARNI

(8) that to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to me/us on this application.

(9) Following are the attachments with this application:

(a) PROVISIONAL specification in triplicate
(b) Form 1 in triplicate
(c) Form 2 in triplicate
(d) Statement and Undertaking on FORM 3 in duplicate
(e) Drawing in triplicate
(f) Abstract

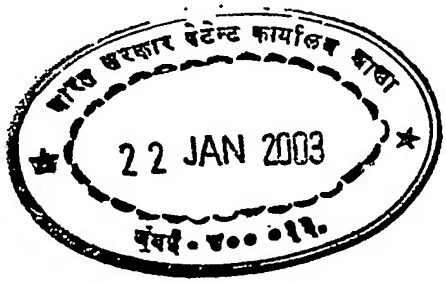
Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No.....
dated..... On .....Bank.

We request that a patent be granted to us for the said invention.

Dated this the 21th day of January 2003

For TORRENT PHARMACEUTICALS LTD.

The Controller of Patents
The Patent Office,
At Mumbai



Form 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(Section 10)

"Novel Dosage Form"

ORIGINAL

We, **Torrent Pharmaceuticals Ltd.**, a company incorporated under the Companies Act, 1956, of Torrent House, Off Ashram Road, Near Dinesh Hall, Ahmedabad-380 009, Gujarat, India,

The following specification particularly describes the invention:

NOVEL DOSAGE FORM

FIELD OF INVENTION

This invention relates to a dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release antidiabetic active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the formulation.

BACKGROUND OF THE INVENTION

Combining two active ingredients in one pharmaceutical unit to improve patient compliance is known in literature. It can be either in the form of two or more active ingredients in immediate release form or a combination of immediate release and modified release form. There are various techniques by which the combination of immediate release and modified release is formulated in single dosage form.

Several examples of formulations having combination of immediate release active ingredient and modified release active ingredient are described below.

Shoichi Higo and Kazuo Igusadescribes in US patent no. 5,985,843 various types of pharmaceutical formulations, which consists of a delayed release of sucralfate and an immediate release fraction of another active ingredient. The pharmaceutical dosage forms are a tablet formulation containing immediate release and delayed release granules; a two or three layer tablet; a tablet with delayed release core surrounded by immediate release shell; a delayed release tablet / granule coated with a film of immediate release active ingredient.

Similarly Jurgen Zeidler et.al describes in US patent No. 6,001,391 a process for producing solid combination tablets, which have atleast two phases. The one of the two phases is processed by melt extrusion technique and contains a water soluble or swellable binder.

Whilst a compressed V-shaped center scored double layer tablet is disclosed by George M. Krause et. al in US patent no. 3,336,200, one layer of which contains immediate

release Active Ingredient and the other layer contains sustained release Active Ingredient. The tablet is divisible in two equal halves.

Similarly Jacob A. Glassman described in US Patent No. 4,503,031 a super fast starting, slow release medicinal tablet, wherein the tablet is comprised of two layers of compressed matrix that are fused together by means of readily dissolvable adhesive substance.

Allan A. Rubin describes in US patent no. 6,238,699 B1 a pharmaceutical dosage form of carbidopa and levodopa where both the Active Ingredients are present as immediate release and sustained release. The formulation is in the form of inlay tablet or bilayered tablet or a capsule containing pellets.

Block Jurgen et. al. describes in PCT application No. WO 01/72286 A1 a formulation of vitamin composition whereas a beadlet comprises a slow release core coated by a controlled release coating. The sustained release core is coated with an immediate release layer.

Richard Ting and Charles Hscao describes in US patent No. 6,372,254 B1 a press coated, pulsatile active ingredient delivery system which comprises a core of immediate release, enveloped by an extended release compartment.

The techniques described above do not work well when the difference in the dose of active ingredients are high for example where the weight ratio of active ingredients in immediate release and modified release is from 1:10 to 1: 15000 and the dose of modified release active ingredient per unit is from500 mg to 1500 mg. The techniques described in the prior art do not give good results when the active ingredient is highly soluble. The weight of the dosage form becomes very high or complicated process for manufacturing is required or accurate dosing of low dose active ingredient is difficult when the techniques reported in the prior art are utilized to make formulation with high dose, high solubility active ingredient in the form of modified release and small dose active ingredient into immediate release form where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg and also it is inconvenient to swallow due to large size.

Accordingly the need exists for a dosage form providing combination of immediate release and modified release

active ingredients and provides solution to problems associated with dosage forms described in prior art. Further, the dosage form should be simple and economical to produce.

Therefore an objective of the present invention is a dosage form of combination of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg.

The second objective of the present invention is a dosage form, which is suitable for swallowing for humans containing two active ingredients one of which is in modified release form and other in immediate release form.

Accordingly, an object of the present invention is to have a dosage form, which uses dual retard technique to control the release of the high dose, high solubility active ingredient and significantly reduce the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing.

A further objective of the present invention is to have a dosage form, containing one active ingredient in an immediate release form and another active ingredient as modified release and the release or disintegration of the immediate release active ingredient is not hindered by the modified release ingredient.

Another objective of the present invention is to provide a dosage form, which effectively avoids the problem of separation of layers of multilayered tablets

A further objective of the present invention is a formulation, which gives accurate dosing and is prepared by conventional and simple processes.

BRIEF DESCRIPTION OF THE INVENTION

The above objects are realized by a dosage form, which is comprised of an inner portion and an outer portion. The inner portion is surrounded by the outer portion in such a manner that only one surface of the inner portion is exposed. The inner portion contains a low dose active ingredient in immediate release form and the outer portion

contains a high dose, high solubility active ingredient as modified release. The weight of the immediate release low dose active ingredient and high dose, high solubility modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg.

The present invention also provides solid oral dosage form comprising a composition according to the invention.

The present invention also teaches the use of dual retard technique to effectively control the release rate of modified release active ingredient by using small quantity of release controlling agents. This dual retard technique thus sufficiently reduces the size of the dosage form, which is convenient for swallowing.

The present invention further teaches the use of hydrophobic release controlling agents, which do not hinder the release of the immediate release active ingredient.

The present invention further provides the dosage form that effectively prevents the problem of separation of the layers of the multilayered tablets.

The present invention further provides a method of treating an animal, particularly a human in need of treatment utilizing the active agents, comprising administering a therapeutically effective amount of composition or solid oral dosage form according to the invention to provide administration of two active ingredients one in immediate release and other in modified release form.

DETAILED DESCRIPTION OF THE INVENTION

The term "modified release" as used herein in relation to the composition according to the invention or a rate controlling polymer or used in any other context means release, which is not immediate release and is taken to encompass controlled release, sustained release, prolonged release, timed release, retarded release, extended release and delayed release. The term "modified release dosage form" as used herein can be described as dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products (as per US FDA guideline for 'SUPAC-MR: Modified Release Solid Oral Dosage Forms').

The term "immediate release" as used herein in relation to composition according to the invention or used in any other context means release which is not modified release and releases more than 70% of the active ingredient within 60 minutes. The term "immediate release dosage form" as used herein can be described as dosage form which allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug (as per US FDA guideline for 'SUPAC-MR: Modified Release Solid Oral Dosage Forms').

The term "dosage form" denotes any form of the formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration.

The term "active ingredient" refers to an agent, active ingredient compound or other substance, or compositions and mixture thereof that provide some pharmacological, often beneficial, effect. Reference to a specific active ingredient shall include where appropriate the active ingredient and it's pharmaceutically acceptable salts.

The term "high dose" as used herein refers to the weight of active ingredient in unit dosage form according to the invention is from 500 mg to 1500 mg.

The term "low dose" as used herein refers to the weight of the active ingredient in unit dosage form according to the invention is less than or equal to 50 mg.

The term "high solubility" as used herein in relation to high dose active ingredient means that from less than 1 part to 30 parts of the water will require dissolving 1 part of active ingredient.

The invention provides a novel dosage form of high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release antidiabetic active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form.

The dosage form comprises of two parts (i) inner portion as an immediate release and (ii) outer portion as modified release. The two parts are compressed together in such a way that one surface of the inner portion is remained exposed and the remaining surfaces are covered by the outer portion.

(i) Inner portion- Inner portion comprises of a low dose active ingredient and includes one or more commonly used excipients in oral immediate release pharmaceutical formulations.

The low dose active ingredient can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Further, the low dose active ingredient, where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

The low dose active ingredient is in the form of immediate release and has dose of 50 mg or less.

The low dose active ingredients are comprises of the following therapeutic classes but not limited to anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthhriics, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, celebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular

agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

Examples of low dose active ingredients comprises of but not limited to zafirlukast, quinapril hydrochloride, isotretinoin, rabeprazole sodium, estradiol(e2), norethindrone acetate, risedronate sodium, pioglitazone HCl, amphetamine, anagrelide hydrochloride, biperiden HCl, mephalan, alprazolam, ramipril, naratriptan hydrochloride, leflunomide, anastrozole, exemestane, paroxetine mesylate, candesartan cilexetil, almotriptan, cerivastatin, betaxolol hydrochloride, bisoprolol fumarate, deloratadine, clonazepam, clorazepate dipotassium, clozapine, methylphenidate HCl, carvedilol, warfarin sodium, norgestrel, ethinyl estradiol, cyclophosphamide, pemoline, liothyronine sodium, misoprostol, tolterodine tartrate, dextroamphetamine sulfate, dicyclomine hydrochloride, digoxin, oxybutynin chloride, doxazosin mesylate, ethacrynate sodium, venlafaxine HCl, enalapril maleate, estradiol, estropipate, famotidine, letrozole, fludrocortisone acetate, fluoxetine, dexmethylphenidate hci, alendronate sodium, ziprasidone, glipizide, glyburide, miglitol, guanabenz acetate, haloperidol, doxercalciferol, zalcitabine, hydrochlorothiazide, hydromorphone HCl, indapamide, estradiol, nitric oxide, ketorolac tromethamine, clonazepam, granisetron, lamotrigine, fluvastatin sodium, levonorgestrel, levothyroxine sodium, atorvastatin calcium, lisinopril, minoxidil, loperamide, loratidine, lorazepam, lovastatin, pravastatin sodium, fluvoxamine maleate, acetaminophen, acyclovir, aminocaproic acid, pitavastatin, rosuvastatin, dalvastatin, , sertraline,pitavastatin,rosuvastatin,dalvastatin,escetalopram, sertraline,celecoxib,parecoxib,valdecoxiband L-6766892.

As indicated above the inner portion of the present invention may comprise auxiliary excipients such as for example diluents, binders, lubricants, surfactants, disintegrants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Suitable diluents include for example pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, starch, dibasic calcium phosphate, saccharides, and/or mixtures of the foregoing. Examples of diluents include microcrystalline celluloses such as those sold under the Trade Mark Avicel PH 101, Avicel PH 102,

Avicel PH 112, Avicel PH 200, Avicel PH301 and Avicel PH 302; lactose such as lactose monohydrate, lactose anhydrous and Pharmatose DCL21 (Pharmatose is a Trade Mark), including anhydrous, monohydrate and spray dried forms; dibasic calcium phosphate such as Emcompress (Emcompress is a Trade Mark); mannitol; Pearlitol SD 200 (Pearlitol SD 200 is a trade mark); starch; sorbitol; sucrose; and glucose.

Suitable binders include for example starch, povidone, hydroxypropylmethylcellulose, pregelatinised starch, hydroxypropylcellulose and/or mixtures of the foregoing.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal slilcon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

Suitable disintegrants include for example lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate and combinations and mixtures thereof.

(ii) **Outer Portion:** The outer portion comprises of a) Micro matrix particles containing high dose, high solubility active ingredient and one or more hydrophobic release controlling agent, b) Coating of Micro matrix particles with one or more hydrophobic release controlling agents. The outer portion may also include one or more commonly used excipients in oral pharmaceutical formulations. The release of the high dose, high solubility active ingredient is controlled through dual retard technique. The dual retard technique is a combination of matrix formulations and reservoir formulations. First the micro matrix particles of high dose, high solubility dose active ingredient and one or more hydrophobic release controlling agents are formed and then these are further coated with one or more release controlling agents. Thus the dual retard release technique presents the double barriers and effectively controls the diffusion of the high dose, high solubility active ingredients from the present invention in predictable manner and also significantly reduces the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing. The other advantages of the present invention are such as it reduces the chances of dose dumping, unnecessary burst

effects and failure of the system, which are otherwise usually associated with simple matrix or reservoir systems.

Further advantages of present invention include the disintegration of inner portion is not hindered as nonswellable release controlling agents are used which do not swell and maintain the shape during operation and it effectively prevents the separation of the layers of the multilayered tablets which is normally associated with normal multilayered tablets.

The high dose, high solubility active ingredient can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Further, the high dose, high solubility active ingredient, where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

The high dose, high solubility active ingredient is in the form of modified release and has dose from 500 mg to 1500 mg.

The high dose, high solubility active ingredients are comprises of the following therapeutic classes but not limited to anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritis, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid

preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors and vertigo agents.

Examples of high dose, high solubility active ingredients comprises of but not limited to potassium chloride, clindamycin, hydroxyurea, erythromycin, lactobionate, vancomycin hydrochloride, balsalazide disodium, sodium valproate, niacin, aminocaproic acid, acetaminophen, Ciprofloxacin, quetiapine. Other drugs suitable for use and meeting the solubility and dose criteria described above will be apparent to those skilled in the art.

As indicated above the outer portion of the present invention may comprise auxiliary excipients such as for example lubricants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal silicon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

In micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:1 to 100:75, more particularly from 100:5 to 100:50, still more preferably from100:7.5 to 100:30 and most preferably from 100:10 to 100:20.

In outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:0.5 to 100:75, more particularly from 100:2.5 to 100:50, still more preferably from100:5 to 100:30 and most preferably from 100:7.5 to 100:20.

According to one embodiment the release controlling agents are pharmaceutically excipients, which are hydrophobic in nature.

The polymers that can be used to form the rate-controlling membrane or micromatrix are described in greater detail herein below.

The hydrophobic release controlling agents are selected from but are not limited to Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, Polyacrylate dispersion 30% as described in Ph. Eur.,Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly (hexyl methacrylate). Poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

According to an especially preferred embodiment the release controlling agents contains ammonio methacrylate co-polymers and fatty acid esters as hereinafter described.

The suitable hydrophobic agents are polymers sold under the Trade Mark Eudragit RS (Ammonio Methacrylate Copolymer type B USP) (, Eudragit NE 30D (Polyacrylate dispersion 30% Ph. Eur.) and Kollicoat SR 30 D and fatty acid esters such as glyceryl behenate, and hydrogenated castor oil. Eudragit polymers are polymeric lacquer substances based on acrylate and/or methacrylates.

The outer portion can also include one or more commonly used excipients in oral pharmaceutical formulations.

Representative commonly used excipients in oral pharmaceutical formulations include talc, fumed silica, glyceryl monostearate, magnesium stearate, calcium stearate, kaolin, colloidal silica, gypsum, Tween 80, Geleol pastiles (trade mark), micronised silica and magnesium trisilicate.

The quantity of commonly used excipients in oral pharmaceutical formulations used is from about 0.5% to

about 200% by weight, preferably from 2 to 100% more particularly 10 to 60% based on the total dry weight of the polymer.

The outer portion can also include a material that improves the processing of the release controlling agents. Such materials are generally referred to as "plasticisers" and include, for example, adipates, azelates, benzoates, citrates, isoebucaes, phthalates, sebacates, stearates, tartrates, polyhydric alcohols and glycols.

Representative plasticisers include acetylated monoglycerides; butyl phthalyl butyl gylcolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate,; ethyl phthalyl ethyl glycolate; glycerin; ethylene glycol, propylene glycol; Triethyl citrate; triacetin; tripropinoin; diacetin; dibutyl phthalate; acetyl monoglyceride; polyethylene glycols; castor oil; triethyl citrate; polyhydric alcohols, acetate esters, glycerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisoctyl trimellitate, diethylexyl phthalate, di-n-octyl phthalate, di-I-octyl phthalate, di-I-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylexyl trimellitate, di-2-ethylexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, glyceryl monocaprylate, glycerol distearate and glyceryl monocaprate.

The amount of plasticiser to be used is from about 1% to 50%based on the weight of the dry release controlling agent(s).

The amount of release controlling agent(s) to be used in forming the outer portion will be determined based on various parameters such as the desired delivery properties, including the amount of active ingredient to be delivered, the active ingredient release rate desired, and the size of the micro matrix particles.

The novel dosage form of the present invention can be manufactured by the following procedure:

A) Inner Portion

The granules of the inner portion can be manufactured in accordance with usual techniques in which the active ingredient and other excipients are mixed and granulated by adding solution of binder in a low or high shear mixer or by fluidized bed granulation. The granulate is dried, preferably in a fluidized bed dryer. The dried granulate is

sieved and mixed with lubricants and disintegrants. Alternatively the manufacture of granules of inner portion can be made by direct mixing of the directly compressible excipients or by roller compaction.

B) Outer Portion

The micro matrix particles of the outer portion can be manufactured in accordance with usual techniques in which the active ingredient and one or more hydrophobic release controlling agents are mixed and granulated by adding solvent in a low or high shear mixer or by fluidized bed granulator. The granulate is dried, preferably in a fluidized bed dryer. The dried granulate is sized. Alternatively the micro matrix particles can be made by extrusion, spheronization or by roller compaction. The micro matrix particles can be coated by a solution of one or more hydrophobic release controlling agents by any known method, including spray application. Spraying can be carried out using a fluidized bed coated (preferably Wurster coating), or in a pan coating system. Alternatively the coating of the micro matrix particles with one or more rate controlling agents can be done by hot melt process using a granulator or fluidized bed coated (preferably Wurster coating), or in a pan coating system.

C) Tablet Compression

The compression of tablets is carried out on usual press coaters (e.g. machines of the Manesty, Cadmach or Kilian) with slight modification. The device such as feed frame and hoppers making top layer are eliminated. The granules of the inner layer are charged in the hopper of the machine compressing first layer and the granules of the outer layer are charged in the hopper of the machine compressing the coating. On operation only the bottom layer of the coating (outer portion) is deposited into the die and the first layer is placed on it. The compression wheels then embed the first layer in the granules of the outer layer, displacing some of latter to form sides, and finally press the whole into the tablet. The resultant tablet has inner portion covered by the outer portion from all the sides except top surface that remains uncovered and the level of the inner portion and the outer portion is same. The tablets can be made of various sizes and shapes. The present invention uses round punch tooling with upper flat bottom punches and lower flat bottom beveled edges lower punches for the compression of inner portion and oblong shaped flat bottom beveled edges punches for the compression of the outer portion.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plan view of the dosage form described in the present invention;

FIG. 2 is an edge view of the dosage form described in the present invention;

FIG. 3 is a transverse section view as seen along the line 3-3 of Fig.1;

FIG. 4 (a) is a cross section of coated micro matrix particles prepared by spheronization and coating for the purpose of illustration only.

FIG. 4 (b) is a cross section of coated micro matrix particles prepared by granulation and coating for the purpose of illustration only.FIG. 5 is a plot of % active ingredient *versus* time for immediate release and modified release active agent;

FIG. 6 is a plot of % active ingredient *versus* time for modified release active agent prepared using dual retard technique as described in the present invention and prepared without retard release technique as per examples 1 and 3;

FIG. 7 is a plot of % active ingredient *versus* time for modified release active agent prepared using dual retard technique as described in the present invention and prepared without retard release technique as per examples 2 and 4.

Referring to FIGS. 1 to 3, a dosage form 4 as described in the present invention having an inner portion 1 containing low dose active ingredient as immediate release and outer portion 2 containing high dose, high solubility active ingredient as modified release. FIG. 4(a)& 4(b) shows the cross section of the coated micro matrix particles 5 and having 6 a high dose, high solubility active ingredient, 7 hydrophobic release controlling agent and 8 a coating of hydrophobic release controlling agent. FIG. 5 shows the release profile of a low dose active ingredient as immediate release 9 and the release profile of a high solubility active ingredient as modified release 10. FIG. 6 and 7 shows release of high dose, high solubility active agent 11 & 12 and 15 & 16 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique as described in the present invention and release of high dose, high solubility active agent 13 & 14 and 17 & 18 as

per example 3 & 4 respectively from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms inspite of that the figures clearly shows that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high dose, high solubility active ingredient for prolonged period.

DIFFERENT MODES FOR PRACTICING THE INVENTION

The following examples further illustrate but by no means limit the present invention.

The dissolution of novel dosage form of the present invention was determined by following method.

For sodium valproate-

Instrument	-	Apparatus I, USP (basket)
Revolution	-	60 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	1000 ml pH 6.8 buffer

For niacin-

Instrument	-	Apparatus I, USP (Basket)
Revolution	-	100 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	900 ml 0.1 N HCl

For lamotrigine-

Instrument	-	Apparatus II, USP (Paddle)
Revolution	-	100 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	1000 ml0.001 N HCl

For pravastatin sodium-

Instrument	-	Apparatus II, USP (Paddle)
Revolution	-	100 / min.
Temperature	-	37±0.5°C
Dissolution medium	-	900 ml pH 6.8 buffer

EXAMPLES

EXAMPLE 1

1) Production of inner portion

11.71 %w/w of pravastatin sodium is mixed with 52.62 %w/w of lactose monohydrate and 22.22 %w/w starch and the mixture is granulated in a binder of 2.22 v povidone in

water and then dried. The granules are sieved and mixed with 1.11 %w/w magnesium stearate, 9.0 g sodium starch glycolate, 0.11 %w/w lake of sunset yellow. This mixture is compressed to 90 mg weight tablets having a diameter of 6.35 mm.

1) Production of outer portion

A) Micro matrix particles- 90.91 vof niacin is mixed with 9.09 %w/w of Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

B) Coating of Micro matrix particles- 85.84 %w/w of micro matrix particles is charged in fluidized bed process of wurster type (manufactured by Glatt, Germany), GPCG-3. 13.61 %w/w of hydrogenated castor oil is dissolved in acetone and this coating solution is sprayed to coat the micro matrix particles. The coated micro matrix particles are sieved and mixed with 0.86 %w/w magnesium stearate.

2) Compression of tablets

Tablet (A)- 90 mg granules of inner portion are pressed to tablets(equal to 10 mg pravastatin) using 6.35 mm round punches and 643 mg granules of outer portion (equal to 500 mg niacin)are compressed using 14.95 X 8.35 mm oblong punches.

Tablet (B)- 90 mg granules of inner portion are pressed to tablets(equal to 10 mg pravastatin) using 6.35 mm round punches and 1286 mg granules of outer portion (equal to 1000 mg niacin)are compressed using 20.3 X 9.8 mm oblong punches.

The compression is done on press coater machine in such a manner that the resultant tablet has inner portion covered by the outer portion from all the sides except top surface that remains uncovered and the level of the inner portion and the outer portion is on the same surface.

The dissolution rate of the novel dosage form was determined (Table 1 and 2)

Table 1: Dissolution profile of tablet (A)

Niacin		Pravastatin sodium	
Time (hour)	% Released	Time (min)	% Released
1	12.4	45	83.8
2	19.1	30	84.1
4	29.4		
6	37.4		

8	41.9		
10	47.1		
12	50.6		
14	54.6		
24	67.7		

Table 2: Dissolution profile of tablet (B)

Niacin		Pravastatin sodium	
Time (hour)	% Released	Time (min)	% Released
1	9.8	45	84.1
2	15.3	60	85.6
4	24.7		
6	28.7		
8	31.4		
10	35.7		
12	39.1		
14	41.9		
24	51.5		

EXAMPLE 2

1) Production of inner portion

38.47 %w/w of lamotrigine is mixed with 2.71 %w/w of crosspovidone and 0.18 %w/w colloidal silicon dioxide and the mixture is granulated in a binder of 0.71 %w/w povidone in water and then dried. The granules are sieved and mixed with 28.70 %w/w of Mannitol (Pearlitol SD 200 R.T.M.), 12.31 %w/w of crosspovidone, 2.31 %w/w of magnesium stearate, 6.15 %w/w aspartame, 2.31 %w/w talc, 5.0 %w/w flavour and 1.15 %w/w of colloidal silicon dioxide. This mixture is compressed to 65 mg weight tablets having a diameter of 5.55 mm.

2) Production of outer portion

A) Micro matrix particles- 90.91 %w/w of sodium valproate is mixed with 9.09 %w/w of Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized.

B) Coating of Micro matrix particles- 85.84 %w/w of micro matrix particles is charged in fluidized bed process of wurster type (manufactured by Glatt, Germany), GPCG-3. 13.61 %w/w of hydrogenated castor oil is dissolved in acetone and this coating solution is sprayed to coat the

micro matrix particles. The coated micro matrix particles are sieved and mixed with 0.86 %w/w magnesium stearate.

3) Compression of tablets

Tablet (A)- 65 mg granules of inner portion are pressed to tablets(equal to 25 mg lamotrigine) using 5.55 mm round punches and 643 mg granules of outer portion (equal to 500 mg sodium valproate)are compressed using 14.95 X 8.35 mm oblong punches.

Tablet (B)- 65 mg granules of inner portion are pressed to tablets(equal to 25 mg lamotrigine) using 5.55 mm round punches and 1286 mg granules of outer portion (equal to 1000 mg sodium valproate)are compressed using 20.3 X 9.8 mm oblong punches. The compression procedure is same as Example 1.

The dissolution rate of the novel dosage form was determined (Table 3 and 4) .

Table 3: Dissolution profile of tablet (A)

Sodium valproate		Lamotrigine	
Time (hour)	% Released	Time (min)	% Released
1	23.3	15	83.5
2	36.3	30	88.6
4	55.1	45	91.6
6	67.5	60	92.8
8	77.0		
10	83.8		
12	88.9		
14	92.5		
24	104.6		

Table 4: Dissolution profile of tablet (B)

Sodium valproate		Lamotrigine	
Time (hour)	% Released	Time (min)	% Released
1	19.0	15	90.3
2	29.5	30	95.6
4	45.2	45	98.3
6	55.9		
8	65.0		
10	71.9		
12	77.8		
14	82.4		
24	95.8		

Dosage forms described in the examples 3 and 4 are prepared by not coating the micro matrix particles of the outer portion but the hydrophobic release controlling agent is mixed with the micro matrix particles. The sole purpose of these examples is to demonstrate the usefulness of the present invention as described earlier. The examples clearly show that the rate of release of the modified release active ingredient is significantly faster than the present invention.

EXAMPLE 3

1) Production of inner portion
Same as for Example 1

2) Production of outer portion
77.76 %w/w of niacin is mixed with 7.78 %w/w of Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.61 %w/w of hydrogenated castor oil and 0.86 %w/w of magnesium stearate.

4) Compression of tablets
Tablet (A)- Same as for Example 1

Tablet (B)- Same as for Example 1

The dissolution rate of the novel dosage form was determined (Table 5 and 6)

Table 5: Dissolution profile of tablet (A)

Niacin		Pravastatin sodium	
Time (hour)	% Released	Time (min)	% Released
1	30.1	45	75.9
2	43.6	60	80.9
4	61.6		
6	74.1		
8	83.9		
10	92.1		
12	99.4		
24	102.6		

Table 6: Dissolution profile of tablet (B)

Niacin		Pravastatin sodium	
Time (hour)	% Released	Time (min)	% Released
1	29.9	45	89.6

2	36.3	60	90.0
4	52.8		
6	63.4		
8	73.5		
10	77.8		
12	84.5		
24	90.5		

EXAMPLE 4

1) Production of inner portion
Same as for Example 2

2) Production of outer portion
77.76 %w/w of sodium valproate is mixed with 7.78 %w/w of Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP) and the mixture is granulated with a solvent mixture of acetone and methylene chloride and then dried. The granules are sized and mixed with 13.61 %w/w of hydrogenated castor oil and 0.86 %w/w of magnesium stearate.

5) Compression of tablets
Tablet (A)- Same as for Example 2

Tablet (B)- Same as for Example 2

The dissolution rate of the novel dosage form was determined (Table 7 and 8)

Table 7: Dissolution profile of tablet (A)

Sodium valproate		Lamotrigine	
Time (hour)	% Released	Time (min)	% Released
1	58.3	15	81.8
2	79.9	30	89.8
4	98.5	45	91.7
6	101.6	60	97.4

Table 8: Dissolution profile of tablet (B)

Sodium valproate		Lamotrigine	
Time (hour)	% Released	Time (min)	% Released
1	50.2	15	86.1
2	69.1	30	87.3
4	91.0	45	92.6
6	101.3	60	98.3

Dated this the 21st day of January 2003.

H. SUBRAMANIAM
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FIG.1

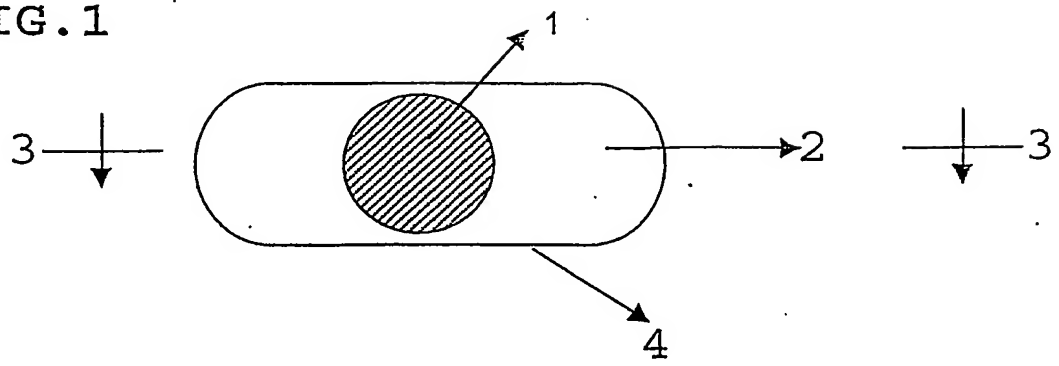

FIG.2

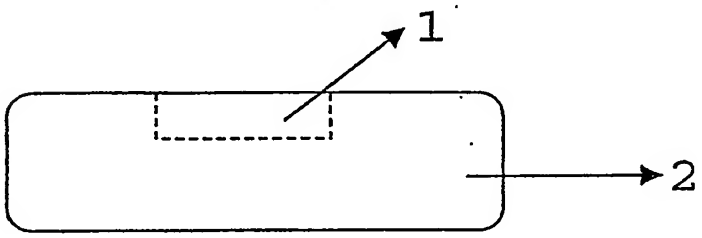

FIG.3

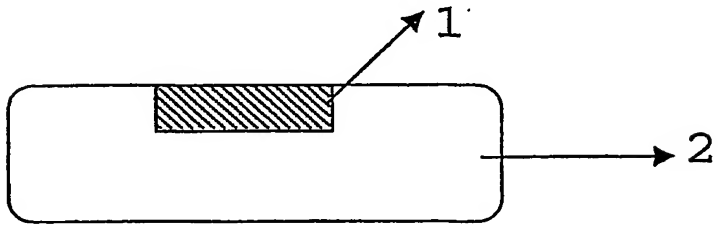

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FIG.4 (a)

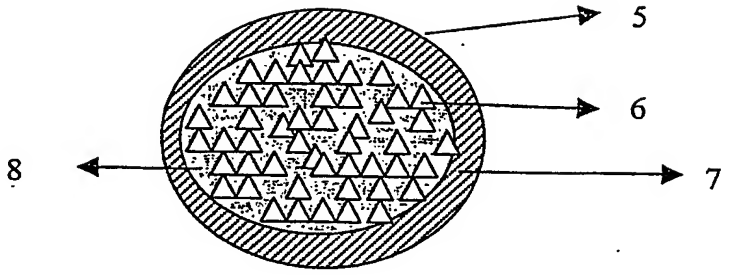

FIG.4 (b)

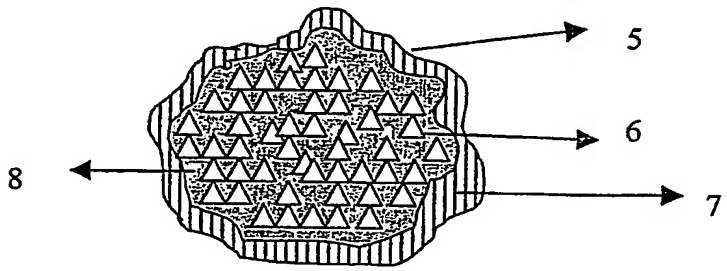

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FIG.5

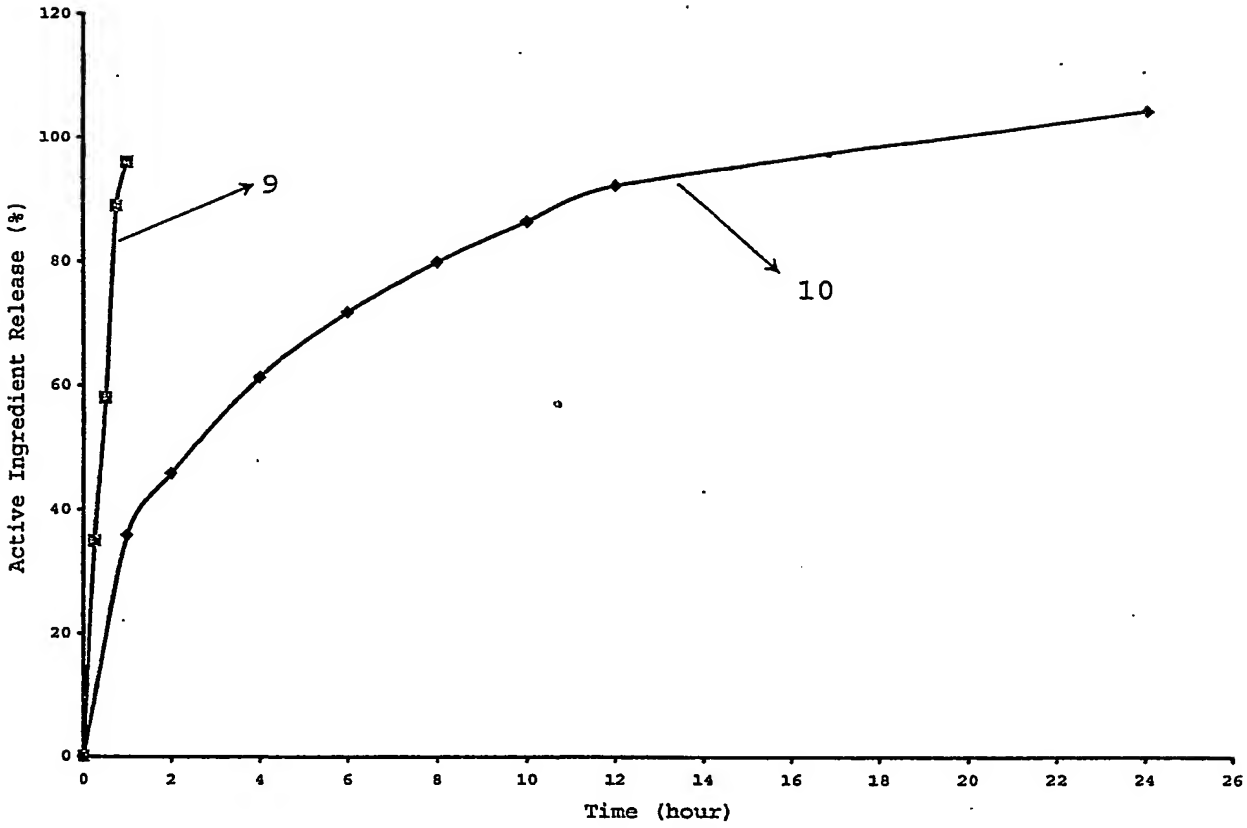

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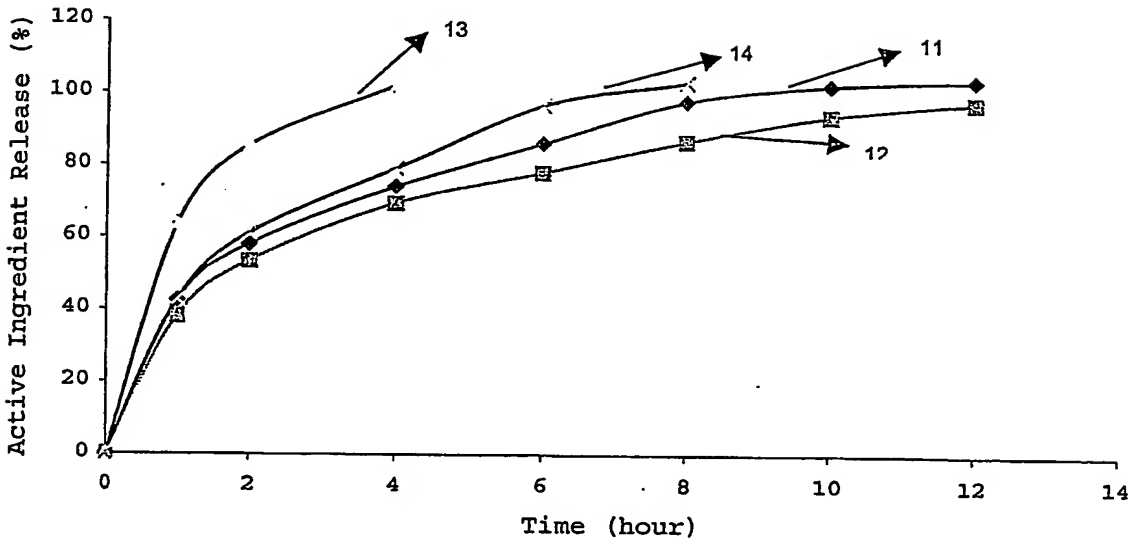
FIG. 6



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